

# TRIAL OF LABOR AFTER ONE CESAREAN: ROLE OF THE ORDER AND NUMBER OF PRIOR VAGINAL BIRTHS ON THE RISK OF EMERGENCY CESAREAN DELIVERY AND NEONATAL ADMISSION

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## SUMMARY

**Objective:** To evaluate the influences of mode of immediate preceding delivery and number of prior vaginal births on the risk of repeat cesarean and neonatal admission at attempted vaginal birth after cesarean.

**Materials and Methods:** We performed a retrospective study of the risk factors for emergency repeat cesarean delivery and neonatal admission in a trial of labor after prior cesarean section. The study comprised 342 women at term with at least one prior vaginal delivery in addition to one previous lower transverse cesarean. Clinical variables with crude  $p < 0.2$  on Fisher's exact test for the defined primary outcomes of repeat cesarean and neonatal admission were included in the model for multivariable logistic regression analysis.

**Results:** Cesarean as the immediate preceding mode of delivery (adjusted odds ratio, 5.3; 95% confidence interval, 2.5–10.8) was an independent predictor of emergency repeat cesarean delivery but not of neonatal admission. Higher parity of two or more previous vaginal deliveries compared with only one prior vaginal delivery was not associated with repeat cesarean or neonatal admission.

**Conclusion:** In women who have had prior vaginal birth attempting a trial of labor after cesarean, a vaginal delivery before cesarean delivery is an independent risk factor for repeat cesarean. Women with two or more prior vaginal births have a similar risk for repeat cesarean and neonatal admission to women with only one prior vaginal birth. [*Taiwan J Obstet Gynecol* 2008;47(3):305–311]

**Key Words:** cesarean section, labor, neonate, vaginal birth after cesarean

## Introduction

The risk of cesarean delivery following an attempt at vaginal birth after cesarean has been found to be lower in women who have had a history of vaginal birth [1–5]. Amongst women who have had a history of vaginal birth and attempting a trial of labor, those with a successful vaginal birth after cesarean (vaginal last) have been found to have a lower risk of repeat emergency cesarean when

compared with women whose vaginal delivery was before the cesarean delivery (cesarean last) [6,7].

Information about the influence of the number of prior vaginal deliveries on the risk of emergency repeat cesarean delivery in a trial of labor is limited. In a low-risk obstetric population, increasing parity was associated with a decreased risk of emergency cesarean delivery [8]. We planned to evaluate whether there might be a similar effect in a trial of labor after cesarean (TOLAC).

As emergency repeat cesarean following TOLAC has been associated with poorer maternal outcome when compared with elective repeat cesarean [9]. Reliable predictors for emergency cesarean delivery will be useful in counseling women considering TOLAC.

As the mode of the previous delivery has been shown to predict the risk of a repeat cesarean [6,7], we sought to investigate its role in neonatal admission. This is



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because neonatal outcome is adversely affected by a failed trial of labor and consequent emergency cesarean delivery [10,11].

We did a PUBMED search (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) in all languages using search terms *previous or prior vaginal delivery* and *neonatal admission* on July 2, 2007. No relevant study was identified concerning prior maternal delivery order in a trial of labor and its effect on neonatal admission, indicating a paucity of information in this area.

## Methods

We performed an analysis to study the effect of mode of last delivery and of an increasing number of previous vaginal deliveries on emergency repeat cesarean and neonatal admission in women with one previous lower transverse cesarean attempting TOLAC. We derived data from a previous study of 1,000 women with one previous lower transverse cesarean that has compared outcomes following a trial of labor with elective repeat cesarean [12]. We identified a subset of 342 women that had at least one prior vaginal birth who underwent TOLAC; these 342 women formed the population for this analysis.

In our previous study [12], the labor ward birth register was searched retrospectively starting from December 31, 2005 backwards to find consecutive cases of women with a singleton fetus at 36–42 weeks' gestation who had a previous cesarean delivery. Case notes were identified and data extracted. We excluded women with more than one previous cesarean, a classical cesarean, an unknown uterine incision, multiple gestations, fetal anomalies, severe preeclampsia, and also repeat cesarean indicated by breech presentation, transverse lie or placenta previa. The 1,000<sup>th</sup> woman who fulfilled the study criteria of one previous transverse lower segment cesarean, but was otherwise suitable for a trial of labor, delivered in June 2002.

Neonates who were admitted to a neonatal unit before hospital discharge were identified through the birth register, maternal case notes and the admission registry of our neonatal unit for the relevant time period. The case notes of admitted babies were retrieved and data extracted.

We categorized the indications for previous cesarean sections into two categories: those indicated by failure to progress in labor, and an "others" group. Failure to progress may be a recurrent condition that can increase the risk of repeat emergency cesarean [4]. We also grouped together the common pregnancy-induced medical disorders of diabetes and hypertension, as these disorders are known to increase the emergency cesarean

rate during a trial of labor [5,13–15]. We defined prolonged labor as a labor of more than 8 hours, as this demarcation represented the 90<sup>th</sup> centile in our study population.

Our hospital conducted about 5,000 deliveries per year with a cesarean delivery rate of about 25%. Our labor ward set-up was compliant with recent major guidelines [16,17] for the conduct of a TOLAC.

Labor induction with vaginal dinoprostone after a previous low transverse cesarean delivery was permitted in our center. Oxytocin augmentation of labor was also permitted at the discretion of senior staff. Women in labor were assessed at least every 4 hours initially and no time limit was set for a trial of labor. An emergency cesarean delivery would be decided on by senior obstetric staff on duty in accordance with usual obstetric practice.

The conduct of this study followed guidelines set out by our institution for a retrospective study. We were exempted from having to obtain individual patient consent.

Data were entered into SPSS version 14 software (SPSS Inc., Chicago, IL, USA). We applied the Student's *t* test to compare means of continuous variables, the Mann-Whitney *U* test to compare ordinal variables, Fisher's exact test to  $2 \times 2$  categorical datasets and multivariable logistic regression analysis to identify independent risk factors. We incorporated all variables with crude  $p < 0.2$  on Fisher's exact test in the multivariable logistic regression analysis. All tests were two-tailed and  $p < 0.05$  was taken as the level of significance.

## Results

Of the 1,000 women with one previous low transverse cesarean that were identified as suitable for a trial of labor, 232 women had elective repeat cesarean, 768 women underwent TOLAC (426 women who had just one lower transverse cesarean and no vaginal delivery were excluded). The subset of 342 women who had at least one prior vaginal birth formed the study group [12]. There were two (0.6%) perinatal deaths but no uterine rupture within this group of 342 women. These rare occurrences precluded meaningful statistical analysis on perinatal death and uterine rupture within our data.

Table 1 shows the characteristics of the study population. There were 51 (14.9%) emergency repeat cesarean deliveries and 19 (4.2%) neonatal admissions within the study group of 342.

The factors analyzed for association with emergency repeat cesarean delivery are shown in Table 2. Nine of 13 factors considered had crude  $p < 0.2$  on Fisher's exact test and were incorporated into a multivariable logistic

**Table 1.** Characteristics of the study population ( $n=342$ )\*

Age (yr)	33.0 ± 4.0
Age ≥ 35 years	113 (33)
Gestational age (wk)	38.9 ± 1.1
Gestation < 40 weeks	233 (68.1)
Parity, median (interquartile range)	2 (1)
Para 3 or greater	158 (46.2)
Cesarean as last delivery	84 (24.6)
Indication for previous cesarean	
Failure to progress in labor	90 (26.3)
Other indications	252 (73.7)
Diabetes or hypertension in pregnancy	62 (18.1)
Prelabor rupture of membranes	23 (6.7)
Induction of labor	
No	305 (89.2)
Vaginal dinoprostone	32 (9.4)
Amniotomy	5 (1.5)
Oxytocin use in labor	96 (28.1)
Epidural analgesia in labor	63 (18.4)
Duration of labor (hr)	4.7 ± 2.5
Labor > 8 hours	35 (10.2)
Meconium stained liquor in labor	18 (5.3)
Male infant	197 (57.6)
Mode of delivery	
Spontaneous vaginal	279 (81.6)
Instrumental vaginal	12 (3.5)
Emergency repeat cesarean	51 (14.9)
Indications for repeat cesarean	
Failure to progress	24 (47.1)
Other indications	27 (52.9)
Neonatal admission <sup>†</sup>	18 (5.3)

\*Data are presented as  $n$  (%) or mean ± standard deviation; <sup>†</sup>includes admission to both special care nursery and intensive care unit.

regression analysis. Following adjustment, a gestation time of less than 40 weeks, cesarean as the last delivery, oxytocin use in labor, labor length more than 8 hours and meconium-stained liquor remained significant predictors of emergency repeat cesarean delivery.

Emergency repeat cesarean delivery was included as a factor for neonatal admission in addition to the aforementioned 13 factors (Table 3). Seven risk factors identified with a crude  $p < 0.2$  were incorporated into a multivariable logistic regression analysis. Following adjustment, maternal diabetes or hypertension, male offspring and emergency repeat cesarean delivery were found to be independently predictive of neonatal admission.

On bivariate analysis, women who underwent TOLAC and had two or more previous vaginal deliveries did not have different outcomes compared with women

who had only one prior vaginal delivery (Tables 1 and 2) with regard to emergency repeat cesarean delivery or neonatal admission.

## Discussion

We found that meconium-stained liquor in labor, cesarean as last delivery, gestational age less than 40 weeks, oxytocin augmentation of labor and a prolonged labor of more than 8 hours were predictive of emergency repeat cesarean delivery in multivariable logistic regression analysis.

Meconium-stained liquor demonstrated the highest adjusted odds ratio (11.4) for emergency repeat cesarean in our study group. Meconium-stained liquor is more frequently encountered in an emergency repeat cesarean delivery than in a primary emergency cesarean delivery [18]. This is likely to be due to meconium-stained liquor being taken as a sign of non-reassuring fetal status with a proportionately larger effect in lowering the threshold for calling off TOLAC compared with when in labor with an unscarred uterus.

Cesarean delivery compared with vaginal delivery as the immediate prior mode of delivery has consistently been reported to be a risk factor for repeat cesarean [6,7], but these studies only considered women with only one vaginal delivery and one previous cesarean. The possible role of a higher number of previous vaginal deliveries was not studied.

Oxytocin use in labor has been shown to be a predictor of a repeat cesarean [1,2,19], similar to our finding. In our study, induction of labor was not associated with emergency cesarean delivery; 32/37 (84.5%) had labor induced by vaginal dinoprostone and only 9/32 (28.1%) of these 32 women required further use of oxytocin in labor, indicating that dinoprostone was highly efficient in inducing labor and vaginal delivery in our multiparous women.

A gestation age of less than 40 weeks was predictive of emergency cesarean in our study; recent reports have shown conflicting results with one showing gestational age < 41 weeks associated with increased risk of emergency repeat cesarean [1] similar to our finding, whilst another has shown the opposite effect [2].

We found prolonged labor of more than 8 hours to be a predictor of emergency repeat cesarean; a foreseeable finding given that 24/51 (47.1%) of the emergency cesarean deliveries in our study were indicated by failure to progress in labor.

We found that two or more previous vaginal deliveries compared with only one prior vaginal delivery (odds ratio, OR, 1.4; 95% confidence interval, CI, 0.8–2.5)

**Table 2.** Risk factors for cesarean delivery\*

	Cesarean delivery (n = 51)	Vaginal delivery (n = 291)	OR <sup>†</sup> (95% CI)	p	AOR <sup>‡</sup> (95% CI)	Adjusted p
Age (yr)	34.1 ± 4.9	32.9 ± 3.9		0.09 <sup>§</sup>		
Age ≥ 35 years	22 (43.1)	91 (31.3)	1.7 (0.9–3.1)	0.11	1.0 (0.5–2.0)	1.0
Gestational age (wk)	38.6 ± 1.1	38.9 ± 1.1		0.017 <sup>§</sup>		
Gestation < 40 weeks	42 (82.4)	191 (65.6)	2.2 (1.1–4.3)	0.022	3.9 (1.5–9.8)	0.004
Parity, median (interquartile range)	3 (2)	2 (1)		0.23 <sup>  </sup>		
Para 3 or greater	27 (52.9)	131 (45.0)	1.4 (0.8–2.5)	0.36		
Cesarean last delivery	26 (51.0)	58 (19.9)	4.2 (2.2–7.8)	< 0.001	5.2 (2.5–10.8)	< 0.001
Indication for previous cesarean						
Failure to progress in labor	14 (27.5)	76 (26.1)	1.1 (0.5–2.1)	0.9		
Others	37 (72.5)	215 (73.9)				
Diabetes or hypertension in pregnancy	14 (27.5)	48 (16.5)	1.9 (1.0–3.8)	0.08	1.6 (0.7–3.9)	0.26
Prelabor rupture of membranes	6 (11.8)	17 (5.8)	2.1 (0.8–5.7)	0.13	1.0 (0.3–3.2)	1.0
Induction of labor	9 (17.6)	28 (9.6)	2.0 (0.9–4.6)	0.14	1.5 (0.5–4.3)	0.49
Oxytocin use in labor	28 (54.9)	68 (23.4)	4.0 (2.2–7.4)	< 0.001	3.4 (1.6–6.9)	0.01
Epidural analgesia in labor	12 (23.5)	51 (17.5)	1.4 (0.8–3.0)	0.33		
Duration of labor (hr)	5.4 ± 2.8	4.6 ± 2.4		0.025 <sup>§</sup>		
Labor > 8 hours	10 (19.6)	25 (8.6)	2.6 (1.1–5.8)	0.024	3.3 (1.3–8.7)	0.015
Meconium stained liquor in labor	10 (19.6)	8 (2.7)	8.6 (3.2–23.1)	< 0.001	11.4 (3.7–34.9)	< 0.001
Male infant	28 (54.9)	169 (58.1)	0.9 (0.5–1.5)	0.76		

\*Data are presented as n (%) or mean ± standard deviation; <sup>†</sup>odds ratio derived using Fisher's exact test; <sup>‡</sup>adjusted odds ratio shown where parameter (crude p < 0.2) was incorporated in the multivariate logistic regression analysis; <sup>§</sup>analysis of means by t test; <sup>||</sup>analysis of nonparametric ordinal data by Mann-Whitney U test. OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio.

**Table 3.** Risk factors for admission to a neonatal unit\*

	Neonatal admission (n = 18)	No neonatal admission (n = 324)	OR <sup>†</sup> (95% CI)	p	AOR <sup>‡</sup> (95% CI)	p
Age (yr)	34.0 ± 4.2	33.0 ± 4.0		0.29 <sup>§</sup>		
Age ≥ 35 years	7 (38.9)	106 (32.7)	1.3 (0.5–3.5)	0.61		
Gestational age (wk)	38.7 ± 1.4	38.9 ± 1.1		0.39 <sup>§</sup>		
Gestation < 40 weeks	13 (72.2)	220 (67.9)	1.2 (0.4–3.3)	0.80		
Parity, median (interquartile range)	3 (1.25)	2 (1)		0.57 <sup>  </sup>		
Para 3 or greater	10 (55.6)	148 (45.7)	1.5 (0.6–3.9)	0.47		
Cesarean last delivery	9 (50.0)	75 (23.1)	3.3 (1.3–8.7)	0.02	2.4 (0.8–7.5)	0.12
Indication for previous cesarean						
Failure to progress in labor	6 (33.3)	84 (25.9)	1.4 (0.5–3.9)	0.58		
Others	12 (66.7)	240 (74.1)				
Diabetes or hypertension in pregnancy	8 (44.4)	54 (16.7)	4.0 (1.5–10.6)	0.007	3.8 (1.2–11.4)	0.019
Prelabor rupture of membranes	3 (16.7)	20 (6.2)	3.0 (0.8–11.4)	0.11	2.4 (0.5–11.5)	0.29
Induction of labor	2 (11.1)	35 (10.8)	1.0 (0.2–4.7)	1.0		
Oxytocin use in labor	8 (44.4)	88 (27.2)	2.1 (0.8–5.6)	0.17	1.0 (0.3–3.4)	1.0
Epidural analgesia in labor	5 (27.8)	58 (17.9)	1.8 (0.6–5.1)	0.34		
Duration of labor (hr)	5.2 ± 2.5	4.7 ± 2.5		0.39 <sup>§</sup>		
Labor > 8 hours	2 (11.1)	33 (10.2)	1.1 (0.2–5.0)	0.71		
Meconium stained liquor in labor	4 (22.2)	14 (4.3)	6.3 (1.8–21.7)	0.01	2.8 (0.6–13.6)	0.21
Male infant	15 (83.3)	182 (56.2)	3.7 (1.1–12.5)	0.027	5.0 (1.3–19.5)	0.022
Emergency repeat cesarean	11 (61.1)	40 (12.3)	11.1 (4.1–30.4)	< 0.001	7.2 (2.0–25.3)	0.002

\*Data are presented as n (%) or mean ± standard deviation; <sup>†</sup>odds ratio derived using Fisher's exact test; <sup>‡</sup>adjusted odds ratio shown where parameter was incorporated in the multivariate logistic regression analysis; <sup>§</sup>analysis of means by t test; <sup>||</sup>analysis of nonparametric ordinal data by Mann-Whitney U test. OR = odds ratio; CI = confidence interval; AOR = adjusted odds ratio.

did not reduce the risk of emergency repeat cesarean delivery. We had anticipated, in extrapolating the data available from a general obstetric population [8], that a higher parity might also be associated with a lower emergency cesarean delivery risk during TOLAC.

Emergency cesarean delivery, male offspring and maternal hypertension or diabetes were found to be predictors of neonatal admission in our study population.

In women without a previous vaginal delivery, emergency repeat cesarean delivery following TOLAC was not associated with neonatal intensive care admission [20]. Our study considered an entirely different population of women who had at least one prior vaginal delivery. In addition, we did not restrict our definition of neonatal admission to admission to the intensive care environment only. These differences might have accounted for our finding of a significant association of emergency cesarean following TOLAC and neonatal admission in contrast to the previous study [20].

Male offspring have been associated with increased morbidity and mortality in preterm births and also with an increased risk of cesarean delivery [21–24]. Our finding of the male neonate as an independent predictor of neonatal admission albeit within a term cohort is broadly consistent with previous findings of poorer perinatal outcome associated with males, but we did not any find an association of male fetuses with emergency repeat cesarean delivery (OR, 0.9; 95% CI, 0.5–1.5).

Neonatal admission associated with maternal diabetes or hypertension has been well described in the general obstetric population, and both maternal conditions are independent predictors of neonatal admission to a neonatal intensive care unit [25]. Our finding is, therefore, compatible with the known effect of maternal diabetes and hypertension on neonatal complications that required admission and might not be specific to a TOLAC.

Our study has a particular limitation; we had only 18 neonatal admissions and our findings are, therefore, vulnerable to both type I and II statistical errors with regard to neonatal admission.

We did not find any evidence to support the proposition that a higher number of previous vaginal deliveries would have a positive impact on the outcome of a trial of labor after one cesarean delivery.

## References

1. Srinivas SK, Stamilio DM, Stevens EJ, Odibo AO, Peipert JF, Macones GA. Predicting failure of a vaginal birth attempt after cesarean delivery. *Obstet Gynecol* 2007;109:800–5.
2. Landon MB, Leindecker S, Spong CY, et al. The MFMU Cesarean Registry: factors affecting the success of trial of labor after previous cesarean delivery. *Am J Obstet Gynecol* 2005;193:1016–23.
3. Grobman WA, Lai Y, Landon MB, et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. *Obstet Gynecol* 2007;109:806–12.
4. Brill Y, Windrim R. Vaginal birth after Caesarean section: review of antenatal predictors of success. *J Obstet Gynaecol Can* 2003;25:275–86.
5. Lehmann M, Hedelin G, Sorgue C, Göllner JL, Grall C, Chami A, Collin D. Predictive factors of the delivery method in women with cesarean section scars. *J Gynecol Obstet Biol Reprod (Paris)* 1999;28:358–68. [In French]
6. Caughey AB, Shipp TD, Repke JT, Zelop C, Cohen A, Lieberman E. Trial of labor after cesarean delivery: the effect of previous vaginal delivery. *Am J Obstet Gynecol* 1998;179: 938–41.
7. Hendler I, Bujold E. Effect of prior vaginal delivery or prior vaginal birth after cesarean delivery on obstetric outcomes in women undergoing trial of labor. *Obstet Gynecol* 2004; 104:273–7.
8. Patel RR, Peters TJ, Murphy DJ. Prenatal risk factors for Caesarean section. Analyses of the ALSPAC cohort of 12,944 women in England. *Int J Epidemiol* 2005;34:353–67.
9. Landon MB, Hauth JC, Leveno KJ, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. *N Engl J Med* 2004;351:2581–9.
10. Hook B, Kiwi R, Amini SB, Fanaroff A, Hack M. Neonatal morbidity after elective repeat cesarean section and trial of labor. *Pediatrics* 1997;100:348–53.
11. Loebel G, Zelop CM, Egan JF, Wax J. Maternal and neonatal morbidity after elective repeat Cesarean delivery versus a trial of labor after previous Cesarean delivery in a community teaching hospital. *J Matern Fetal Neonatal Med* 2004;15: 243–6.
12. Tan PC, Subramaniam RN, Omar SZ. Labour and perinatal outcome in women at term with one previous lower segment Caesarean: a review of 1000 consecutive cases. *Aust N Z J Obstet Gynaecol* 2007;47:31–6.
13. Coleman TL, Randall H, Graves W, Lindsay M. Vaginal birth after cesarean among women with gestational diabetes. *Am J Obstet Gynecol* 2001;184:1104–7.
14. Srinivas SK, Stamilio DM, Stevens EJ, Peipert JF, Odibo AO, Macones GA. Safety and success of vaginal birth after cesarean delivery in patients with preeclampsia. *Am J Perinatol* 2006;23:145–52.
15. d'Orsi E, Chor D, Giffin K, et al. Factors associated with vaginal birth after cesarean in a maternity hospital of Rio de Janeiro. *Eur J Obstet Gynecol Reprod Biol* 2001;97:152–7.
16. Society of Obstetricians and Gynaecologists of Canada. SOGC clinical practice guidelines. Guidelines for vaginal birth after previous caesarean birth. Number 155 (replaces guideline Number 147), February 2005. *Int J Gynaecol Obstet* 2005;89:319–31.
17. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 54. Vaginal birth after previous cesarean. *Obstet Gynecol* 2004;104:203–12.
18. Stone J, Lockwood CJ, Berkowitz GS, Lynch L, Alvarez M, Lapinski RH, Berkowitz RL. Morbidity of failed labor in

- patients with prior cesarean section. *Am J Obstet Gynecol* 1992;167:1513-7.
19. Grobman WA, Gilbert S, Landon MB, et al. Outcomes of induction of labor after one prior cesarean. *Obstet Gynecol* 2007;109:262-9.
  20. Durnwald C, Mercer B. Vaginal birth after Cesarean delivery: predicting success, risks of failure. *J Matern Fetal Neonatal Med* 2004;15:388-93.
  21. Yu VY, Loke HL, Bajuk B, Szymonowicz W, Orgill AA, Astbury J. Prognosis for infants born at 23 to 28 weeks' gestation. *Br Med J (Clin Res Ed)* 1986;293:1200-3.
  22. Draper ES, Manktelow B, Field DJ, James D. Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ* 1999;319:1093-7.
  23. Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? *Gend Med* 2007;4:19-30.
  24. Costeloe K, Hennessy E, Gibson AT, Marlow N, Wilkinson AR. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* 2000;106:659-71.
  25. Ross MG, Downey CA, Bemis-Heys R, Nguyen M, Jacques DL, Stanziano G. Prediction by maternal risk factors of neonatal intensive care admissions: evaluation of > 59,000 women in national managed care programs. *Am J Obstet Gynecol* 1999;181:835-42.